



Risk of Pregnancy in Moderate and Severe Aortic Stenosis: From the Multinational ROPAC Registry

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Abstract: BACKGROUND Controversial results on maternal risk and fetal outcome have been reported in women with aortic stenosis (AS). OBJECTIVES The authors sought to investigate maternal and fetal outcomes in patients with AS in a large cohort. METHODS The Registry on Pregnancy and Cardiac Disease (ROPAC) is a global, prospective observational registry of women with structural heart disease, providing a uniquely large study population. Data of women with moderate (peak gradient 36 to 63 mm Hg) and severe AS (peak gradient ≥ 64 mm Hg) were analyzed. RESULTS Of 2,966 pregnancies in ROPAC, the authors identified 96 women who had at least moderate AS (34 with severe AS). No deaths were observed during pregnancy and in the first week after delivery. However, 20.8% of women were hospitalized for cardiac reasons during pregnancy. This was significantly more common in severe AS compared with moderate AS (35.3% vs. 12.9%; $p = 0.02$), and reached the highest rate (42.1%) in severe, symptomatic AS. Pregnancy was complicated by heart failure in 6.7% of asymptomatic and 26.3% of symptomatic patients, but could be managed medically, except for 1 patient who was symptomatic before pregnancy and underwent balloon valvotomy. Children of patients with severe AS had a significantly higher percentage of low birth weight (35.0% vs. 6.0%; $p = 0.006$). CONCLUSIONS Mortality in pregnant women with AS, including those with severe AS, appears to be close to zero in the current era. Symptomatic and severe AS does, however, carry a substantial risk of heart failure and is associated with high rates of hospitalization for cardiac reasons, although heart failure can nearly always be managed medically. The results highlight the importance of appropriate pre-conceptional patient evaluation and counseling.

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Risk of Pregnancy in Moderate and Severe Aortic Stenosis

From the Multinational ROPAC Registry

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ABSTRACT

BACKGROUND Controversial results on maternal risk and fetal outcome have been reported in women with aortic stenosis (AS).

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve
replacement

ESC = European Society of
Cardiology

IQR = interquartile range

NYHA = New York Heart
Association

OR = odds ratio

WHO = World Health
Organization

Pregnancy carries a very low risk of death in developed countries, but overall, cardiac reasons remain the leading cause of maternal mortality (1). Consistent with this, women with pre-existing heart disease have 100 times greater mortality than normal (2). Pregnancy is associated with profound changes in hemodynamic parameters, perhaps explaining why pre-existing heart disease has such an adverse impact on morbidity and mortality in pregnant women (3). Although there is clear evidence that pregnancy is a high-risk endeavor in women with complex heart disease, and especially those with severe pulmonary hypertension (4,5), available data are limited in women with less complex heart disease. Obstructive heart lesions will be aggravated by the increase in stroke volume occurring with pregnancy, and are therefore of particular concern. Aortic stenosis (AS) is one of these lesions, but it is relatively uncommon in women of childbearing age. However, when present, it has been reported to be associated with an increased risk of maternal cardiovascular events, including death, obstetric morbidity (such as pre-term birth), and fetal complications, including growth restriction, miscarriage, and stillbirth (6). The evidence in this setting is nevertheless limited, and the results of published reports are conflicting. Unfortunately, prior studies either encompassed all forms of heart disease (7,8) or included mild AS (9). In addition, some series report on historic patient cohorts (6). As a consequence, the reported maternal mortality rate ranges between 2% and 17.4%, and the risk in contemporary cohorts of women presenting with severe AS remains unclear (6,9).

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The purpose of this study was therefore to investigate maternal and fetal adverse events in contemporary patients with moderate or severe AS on the basis of a prospective observational study of a large number of pregnancies in patients with AS included in ROPAC (Registry of Pregnancy and Cardiac Disease).

METHODS

ROPAC is a global, prospective, observational registry of women with heart disease. It was initiated by the European Society of Cardiology (ESC) working groups on congenital heart disease and valvular heart disease, and is part of the EURObservational Research Programme of the ESC. The registry allows for the inclusion of patients with structural or ischemic

heart disease, aortic pathology, and pulmonary hypertension. The registry started in January 2008. Patients who were pregnant in 2007 could also be included retrospectively; from January 2008, patients were included prospectively. Patients were managed at the discretion of the attending physicians. The overall mortality during pregnancy and until 1 week after delivery in the registry has been reported at 1%. Further details on the registry and the institutional review board/ethical approval have previously been published (2,10). The current study is covered by approval under the umbrella of the general ROPAC project.

The present study retrospectively analyzed the outcome and complications in pregnant women with moderate or severe AS included in the registry up to April 2014. We focused exclusively on women with moderate or severe AS. Patients with additional congenital or acquired heart disease (with the exception of simple corrected pre-tricuspid shunts, aortic coarctation) were not included in the current study. The severity of AS was graded on the basis of available transthoracic echocardiographic data at baseline. Moderate AS was defined as a peak transaortic gradient ≥ 36 mm Hg (corresponding to a peak velocity ≥ 3 m/s), whereas severe AS was defined as a peak aortic gradient ≥ 64 mm Hg (corresponding to a peak velocity ≥ 4 m/s) using the simplified Bernoulli equation (11,12). This is in agreement with current guidelines and general recommendations for assessing the severity of AS in the presence of normal flow rate (13). Patients who had undergone aortic valve replacement before pregnancy were included if they fulfilled the hemodynamic criteria described in the preceding text. However, further analyses were also performed and presented separately because prosthetic valve-related risks require additional consideration. Repeated pregnancies were excluded from the analysis.

Baseline characteristics included maternal age, general cardiovascular risk factors, major noncardiac disease, cardiac diagnosis, prior interventions, cardiac symptoms, medication, and obstetric history. Heart failure before pregnancy was defined according to current guidelines clinically as a syndrome in which patients have typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) (14). Maternal mortality was defined as death during pregnancy or up to 1 week after delivery. Miscarriage was defined as loss of pregnancy up to 24 weeks of gestation or a fetus weighting <500 g, whereas fetal mortality was defined as fetal loss beyond 24 weeks of pregnancy. Outcome measures included maternal mortality,

maternal hospital admission (all-cause and admission for cardiac reasons), pre-term labor (<37 weeks of gestation), neonatal mortality (neonatal death <30 days postpartum), low birth weight (defined as a birth weight <2,500 g according to World Health Organization [WHO] criteria), small for gestational age neonates (weight below the 10th percentile for gestational age), and the need for Cesarean section.

STATISTICAL ANALYSIS. Data are presented as numbers (percentage) for categorical variables or mean \pm SD or median (interquartile range [IQR]: 25th to 75th percentile) for continuous variables, depending on data distribution. Groups were compared with the use of chi-square tests, Student *t* tests, or nonparametric Mann-Whitney *U* tests, respectively. The relation between baseline parameters and outcome was assessed with the use of univariable and multivariable logistic regression analyses, and odds ratios (ORs) with 95% confidence intervals are provided. Models were built by including significant univariable parameters into a multivariable analysis. For all analyses, a 2-tailed *p* value <0.05 was used as the criterion for statistical significance. Analyses were performed with the use of Medcalc statistical software version 14.12.0 (Medcalc Software, Ostend, Belgium).

RESULTS

BASILINE CHARACTERISTICS. Using the ROPAC registry, which included 2,966 pregnancies from 99 centers in 40 countries (enrolled between 2008 and 2014), we identified women with at least moderate AS, who had adequate baseline echocardiographic data. After exclusion of 3 patients with associated significant congenital heart disease (1 with ventricular septal defect, 1 with Tetralogy of Fallot, and 1 with a double outlet right ventricle), 96 women remained and were included in the study. Echocardiographic baseline investigations were performed at a mean of 52 ± 347 days before conception in these patients. Of these, 44% were performed before conception. No significant difference in the mean peak aortic gradient was seen between patients with and without pre-conceptional echocardiographic assessment (59 ± 22 mm Hg vs. 64 ± 29 mm Hg; *p* = 0.33). Overall, 22 women already had 1 child, 17 women had 2 children, and 13 had 3 or more children. Baseline maternal characteristics are presented in [Table 1](#). The median age at pregnancy was 30 years. Before pregnancy, 62.5% of AS patients were asymptomatic, whereas 33.3% were classified as New York Heart Association (NYHA) functional class II and 4.2% as NYHA functional class III. Approximately 50% of patients had a previous successful pregnancy. Stratifying patients

by the severity of the underlying AS revealed that the 34 women with severe AS were more likely to be symptomatic or to have pre-existing heart failure symptoms ([Table 1](#)). In the current study, bicuspid aortic valve was the most prevalent etiology for AS (53.5%). In addition, 18 patients had rheumatic aortic valve disease. None of the patients had connective tissue disorders, such as Marfan or Ehlers-Danlos syndrome. Two patients had aortic dilation (45 mm and 50 mm aortic diameter). In total, 12 patients had repaired aortic coarctation (9 with bicuspid aortic valve). The mean peak aortic gradient was 62.1 ± 26.3 mm Hg, whereas the mean aortic gradient was 39.1 ± 17.9 mm Hg. With the exception of 1 woman with an ejection fraction of 39%, all patients had normal left ventricular systolic function.

Overall, 8 patients had a previously implanted bioprosthesis (7 in the aortic position, 1 in the mitral position). Of these, only the patient with the mitral bioprosthesis had severe native AS (peak gradient 71 mm Hg, mean gradient 49 mm Hg), whereas the patients with aortic bioprostheses exhibited only moderate AS (peak gradient 47.1 ± 6.5 mm Hg, mean gradient 28.1 ± 5.4 mm Hg). In addition, 13 patients had a previously implanted mechanical heart valve (4 in the mitral position, 10 in the aortic position, and 1 in both positions). The peak and mean Doppler gradients in those patients with a mechanical aortic valve were 64.4 ± 26.7 mm Hg and 39.0 ± 20.2 mm Hg, respectively. Anticoagulation was performed with oral vitamin K antagonists throughout pregnancy or staged therapy with low molecular weight heparin during the first trimester, followed by vitamin K antagonists in 10 patients. Low molecular weight heparin was used throughout pregnancy in 3 patients. None of the patients in the entire cohort developed a valve thrombosis, including those with a mechanical aortic valve.

MATERNAL CARDIAC COMPLICATIONS. No patient died during pregnancy or within 1 week postpartum. However, cardiovascular events and hospitalizations were common. Overall, 35.8% of patients had at least 1 hospital admission during pregnancy, with 20.8% admitted for cardiac reasons ([Table 2](#)). Women with severe AS were significantly more likely to be admitted during pregnancy (35.3% cardiac admissions) than those with only moderate AS (12.9%, *p* = 0.02). Heart failure, first hospital admission for cardiac reasons, and hospital admissions for all reasons occurred at a mean gestational time of 27.2 ± 7.5 weeks, 24.3 ± 9.7 weeks, and 26.9 ± 9.5 weeks, respectively. The highest rate of hospitalization for cardiac reasons was seen in symptomatic severe AS patients, with a rate of 42.1%. Pregnancy was

	All AS Patients	Moderate AS	Severe AS	p Value	Asymptomatic Patients	Symptomatic Patients	p Value
Number of patients	96	62	34		60	36	
Age in yrs	30.3 (26.0–32.8)	29.8 (26.3–32.9)	30.6 (25.9–32.7)	0.96	30.5 (26.2–33.4)	29.9 (25.8–32.8)	0.67
Nulliparous	47 (49)	36 (58.1)	11 (32.4)	0.028	36 (60)	11 (30.6)	0.01
Prior cardiac intervention	48 (50)	34 (54.8)	14 (41.2)	0.11	30 (50.0)	18 (50)	0.83
NYHA functional class							
I	60 (62.5)	45 (72.6)	15 (44.1)	0.02	60 (100)	—	—
II	32 (33.3)	15 (24.2)	17 (50.0)		—	32 (88.9)	
III	4 (4.2)	2 (3.2)	2 (5.9)		—	4 (11.1)	
IV	0 (0)	0 (0)	0 (0)		—	0 (0)	
AS location							
Valvular	59 (61.5)	45 (72.6)	18 (52.9)	0.02	35 (58.3)	24 (66.7)	0.49
Subvalvular	22 (22.9)	11 (17.7)	11 (32.4)		16 (26.7)	6 (16.7)	
Supravalvular	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Not specified	15 (15.6)	10 (16.1)	5 (14.7)		9 (15.0)	6 (16.7)	
Bicuspid aortic valve	46 (53.5)	34 (60.7)	12 (40.0)	0.18	35 (64.8)	11 (34.4)	0.02
Peak aortic gradient, mm Hg	62.1 ± 26.3	47.5 ± 6.9	88.7 ± 28.0	<0.0001	56.8 ± 20.1	71.1 ± 32.7	0.006
Mean aortic gradient, mm Hg	39.1 ± 17.9	27.8 ± 5.3	55.1 ± 17.4	<0.0001	35.4 ± 16.0	44.3 ± 19.5	0.006
Left ventricular function	65.6 ± 8.7	67.4 ± 6.2	62.4 ± 11.5	0.27	66.6 ± 7.1	64.0 ± 10.7	0.60
Hypertension	11 (11.5)	9 (14.5)	2 (5.9)	0.35	6 (10)	5 (13.9)	0.80
Smoker, current or previous	11 (12.8)	8 (14.0)	3 (10.3)	0.73	7 (12.5)	4 (13.3)	0.73
Diabetes	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Pre-existing heart failure symptoms	13 (13.5)	3 (4.8)	10 (29.4)	0.002	0 (0)	13 (36.1)	<0.0001
Cardiac medication	14 (35.9)	9 (34.6)	5 (38.4)	0.91	8 (33.3)	6 (40.0)	0.94
Beta-blocker	7 (12.5)	4 (11.1)	3 (15.0)	0.22	5 (13.9)	2 (10.0)	0.56
ACE inhibitor/ARB	3 (5.4)	2 (5.6)	1 (5.0)	0.60	1 (2.8)	2 (10.0)	0.60
Anticoagulation	11 (19.6)	9 (33.3)	2 (10.0)	0.68	8 (22.2)	3 (15.0)	0.53

Values are n, median (IQR), n (%), or mean ± SD. p Values refer to differences between patients with moderate and severe AS or asymptomatic and symptomatic patients, respectively. p Values in **bold** are statistically significant.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AS = aortic stenosis; IQR = interquartile range; NYHA = New York Heart Association.

complicated by heart failure in 6.7% of patients asymptomatic before pregnancy and in 26.3% of symptomatic patients with severe AS.

The leading cardiac complications were new or worsening heart failure during pregnancy and arrhythmias. By contrast, cerebrovascular complications or pulmonary embolism were not recorded in this cohort, and only 1 patient was reported to have developed endocarditis during pregnancy.

Heart failure could be managed medically in all patients, except for 1 case undergoing aortic valvotomy. This patient, with a history of 2 previous pregnancies, was unaware of the severe AS, although she had suffered from severe dyspnea after a previous delivery. She presented with critical AS and heart failure at 20 weeks of gestation, and had impaired left ventricular systolic function. Aortic valvuloplasty was performed, resulting in a reduction in both peak and mean gradients from 156 and 71 mm Hg pre-intervention to 113 and 55 mm Hg post-intervention, respectively, and in moderate aortic regurgitation. The further course of the pregnancy and delivery was uneventful.

The patient delivered a 3,200-g baby vaginally at 38 weeks. However, 1 month after delivery, the patient presented again with severe symptoms and underwent aortic valve replacement (AVR).

One patient underwent AVR with a mechanical prosthesis during pregnancy as a consequence of aortic valve endocarditis at 4 months into pregnancy. The further course of the pregnancy was uneventful in this patient, with a vaginal delivery at 38 weeks.

OBSTETRIC AND FETAL OUTCOMES. Median pregnancy duration was 38.6 (IQR: 37.2 to 39.8) weeks, and was significantly shorter in patients with severe AS (37.9 [IQR: 35.2 to 39.0] weeks vs. 39.0 [IQR: 38.0 to 40.0] weeks; $p = 0.001$) (Table 2). Women with severe AS also had a significantly higher rate of Cesarean section compared with those with moderate AS (75.0% vs. 48.3%; $p = 0.008$). The main reason for Cesarean section was a cardiac indication, recorded in 65.9% of patients. A low Apgar score (below 7) was present in 9.0% of neonates (5.2% vs. 16.1% of patients with

TABLE 2 Maternal and Fetal Outcomes

	All AS Patients	Moderate AS	Severe AS	p Value	Asymptomatic Patients	Symptomatic Patients	p Value
Maternal mortality	0	—	—	—	—	—	—
Maternal hospital admission	34 (35.8)	17 (27.4)	17 (51.5)	0.027	21 (35.0)	13 (37.1)	0.42
Maternal cardiac hospital admission	20 (20.8)	8 (12.9)	12 (35.3)	0.02	9 (15.0)	11 (30.6)	0.12
Cardiac complications							
Heart failure	11 (11.5)	5 (8.1)	6 (17.6)	0.29	5 (8.3)	6 (16.7)	0.36
Arrhythmias (SVT)	1 (1.0)	1 (1.6)	0 (0)	0.76	1 (1.7)	0 (0)	0.80
Arrhythmias (VT/VF)	1 (1.0)	0 (0)	1 (2.9)	0.76	0 (0)	1 (2.8)	0.79
Endocarditis	1 (1.0)	1 (1.6)	0 (0)	0.76	1 (1.7)	0 (0)	0.80
Valve thrombosis	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Cerebrovascular complication	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Pulmonary embolism	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Deep venous thrombosis	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Obstetric complications							
Pregnancy-induced hypertension	3 (3.2)	2 (3.2)	1 (3.0)	0.57	2 (3.3)	1 (2.9)	0.63
(Pre-)eclampsia	3 (3.2)	3 (4.8)	0 (0)	0.50	3 (5.0)	0 (0)	0.46
Cesarean section	54 (57.4)	30 (48.3)	24 (75.0)	0.008	30 (50.0)	24 (70.6)	0.029
Hemorrhagic events	4 (4.2)	4 (6.5)	0 (0)	0.33	4 (6.7)	0 (0)	0.29
Fetal outcome							
Apgar score <7	8 (9.0)	3 (5.2)	5 (16.1)	0.21	4 (7.0)	4 (12.5)	0.37
Pregnancy duration (weeks)	37.2 ± 5.2	38.0 ± 4.4	35.5 ± 6.4	0.002	37.0 ± 6.2	37.5 ± 2.8	0.08
Pre-term birth <37 weeks	18 (20.9)	8 (16.0)	10 (35.7)	0.017	10 (18.2)	8 (25.8)	0.49
Mean birth weight, g	3,010 ± 691	3,198 ± 549	2,648 ± 797	0.003	3,091 ± 642	2,878 ± 758	0.24
Low birth weight (<2,500 g)	16 (16.2)	4 (6.0)	12 (35.0)	0.006	6 (10.0)	10 (27.8)	0.037
Small for gestational age	8 (9.3)	2 (3.4)	6 (21.4)	0.022	3 (5.5)	5 (16.1)	0.21
Miscarriages	2 (2.1)	2 (3.2)	0 (0)	0.76	2 (3.3)	0 (0)	0.71
Fetal death	0 (0)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Neonatal death	1 (1.1)	0 (0)	1 (3.3)	0.05	0 (0)	1 (3.0)	0.38

Values are n (%) or mean ± SD. p Values refer to differences between patients with moderate and severe AS or asymptomatic and symptomatic patients, respectively. p Values in **bold** are statistically significant.

AS = aortic stenosis; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

moderate and severe AS, respectively; $p = 0.21$). Children of patients with severe AS had significantly lower birth weight (3,200 g [IQR: 2,932 to 3,490 g] vs. 3,000 g [IQR: 2,145 to 3,227 g]; $p = 0.0025$).

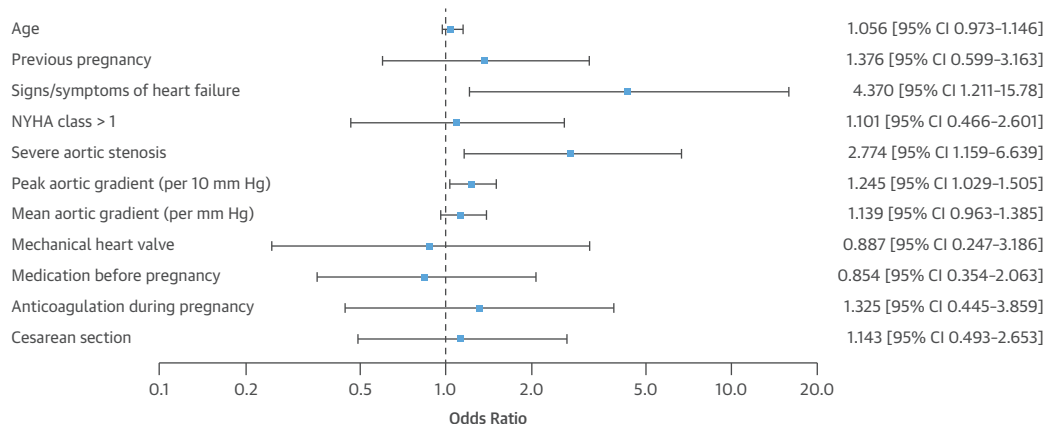
There were 2 miscarriages (both in moderate AS), no fetal losses between 24 weeks and delivery, and 1 neonatal death (in severe AS). The neonatal death occurred after a pregnancy duration of 30 weeks and 2 days. The child that died was delivered by Cesarean section, and was small for gestational duration, with a weight of 1,000 g. The exact reason for delivery was not documented, but the child died due to respiratory distress syndrome. This event occurred in a mother with severe AS, who had a previous unsuccessful pregnancy complicated by heart failure and arrhythmias.

PREDICTORS OF MATERNAL OR FETAL COMPLICATIONS. Figures 1 to 3 present predictors of adverse maternal or fetal outcome. As illustrated in Figure 1, the OR of hospitalization in women with severe AS was 2.77 compared with those with only moderate AS. In

addition, peak aortic gradient on transthoracic echocardiography was significantly associated with a higher risk of maternal hospitalization during pregnancy (OR: 1.245/10 mm Hg; $p = 0.024$). On multivariable analysis, peak aortic gradient emerged as an independent predictor of maternal outcome. Regarding fetal outcome, severity of AS and peak aortic gradient on echocardiography again proved to be independent predictors of low birth weight (Figure 2) and small for gestational age neonates, respectively (Figure 3).

DIFFERENCES BETWEEN COUNTRIES OF THE EUROPEAN UNION/UNITED STATES, AND NON-EUROPEAN UNION COUNTRIES. Seventy-four pregnancies were reported from inside the European Union or the United States (Group A), and 25 from outside (Group B). Group B included 16 cases from Egypt, 5 from the Russian Federation, 2 from the Arab Emirates, and 1 each from Turkey and Serbia/Montenegro. Comparing the 2 cohorts revealed no significant differences between the groups regarding the severity of AS

FIGURE 1 Predictors of Adverse Maternal Outcome



Forrest plots illustrating the results of the univariate logistic regression analysis for adverse maternal outcome, defined as hospital admission during pregnancy. Severe aortic stenosis and the peak aortic gradient were significantly related to worse outcome. An **asterisk** denotes significant results. CI = confidence interval; NYHA = New York Heart Association.

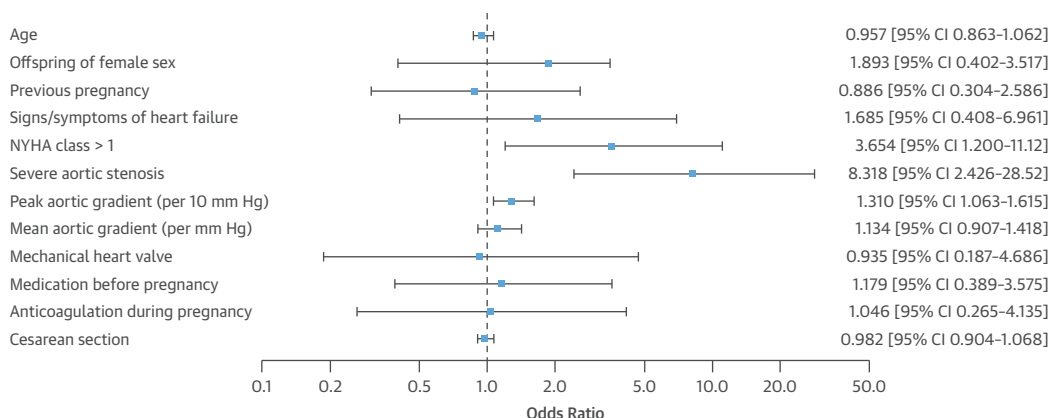
(severe AS 28.3% in group A vs. 52.0% in group B countries; $p = 0.057$), the peak aortic gradient (group A 59.7 ± 25.8 mm Hg vs. group B 68.4 ± 25.9 mm Hg; $p = 0.16$) or the mean aortic gradient (group A 37.4 ± 18.1 mm Hg vs. group B 42.9 ± 16.6 mm Hg; $p = 0.11$). Women from Group B countries were, however, more frequently symptomatic at baseline (56.0% vs. 29.7%; $p = 0.034$) and had more hospital admissions during pregnancy (52.0% vs. 30.1%; $p = 0.049$ overall, and 48.0% vs. 12.2%; $p = 0.0005$ for cardiac reasons)

compared with those from Group A countries. The rate of fetal complications, such as small for gestational age (group A 9.4% vs. group B 9.1%; $p = 0.70$) and pre-term birth (group A 21.7% vs. group B 14.3%; $p = 0.40$) was similar between the cohorts.

DISCUSSION

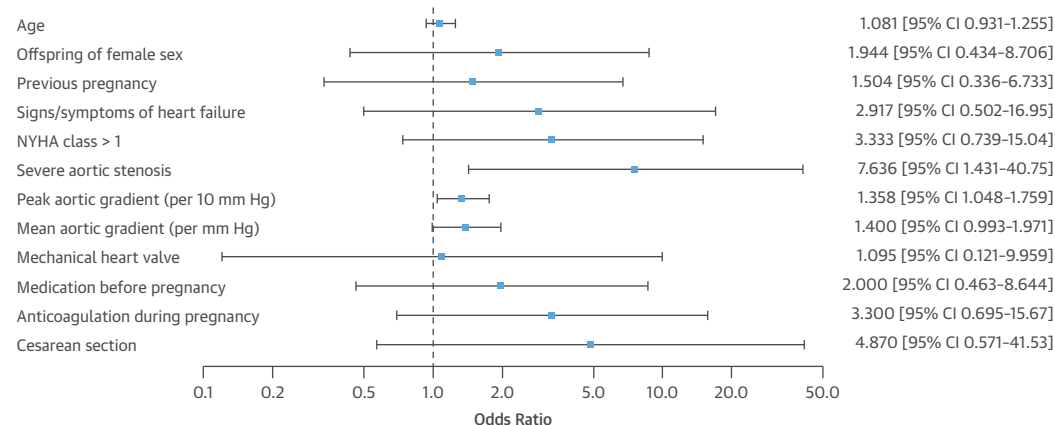
The current registry-based study suggests that mortality risk in pregnant women with AS, including

FIGURE 2 Predictors of Low Birth Weight



Forrest plots illustrating the results of the univariate logistic regression analysis for adverse fetal outcome (low birth weight, defined as birth weight <2,500 g). Severe aortic stenosis, peak aortic gradient, and NYHA class >1 at baseline were predictive of worse fetal outcome. An **asterisk** denotes significant results. Abbreviations as in Figure 1.

FIGURE 3 Predictors of Small for Gestational Age Infants



Forest plots illustrating the results of the univariate logistic regression analysis for adverse fetal outcome (small for gestational age). Severe aortic stenosis and peak aortic gradient were predictive of worse fetal outcome. An **asterisk** denotes significant results. Abbreviations as in Figure 1.

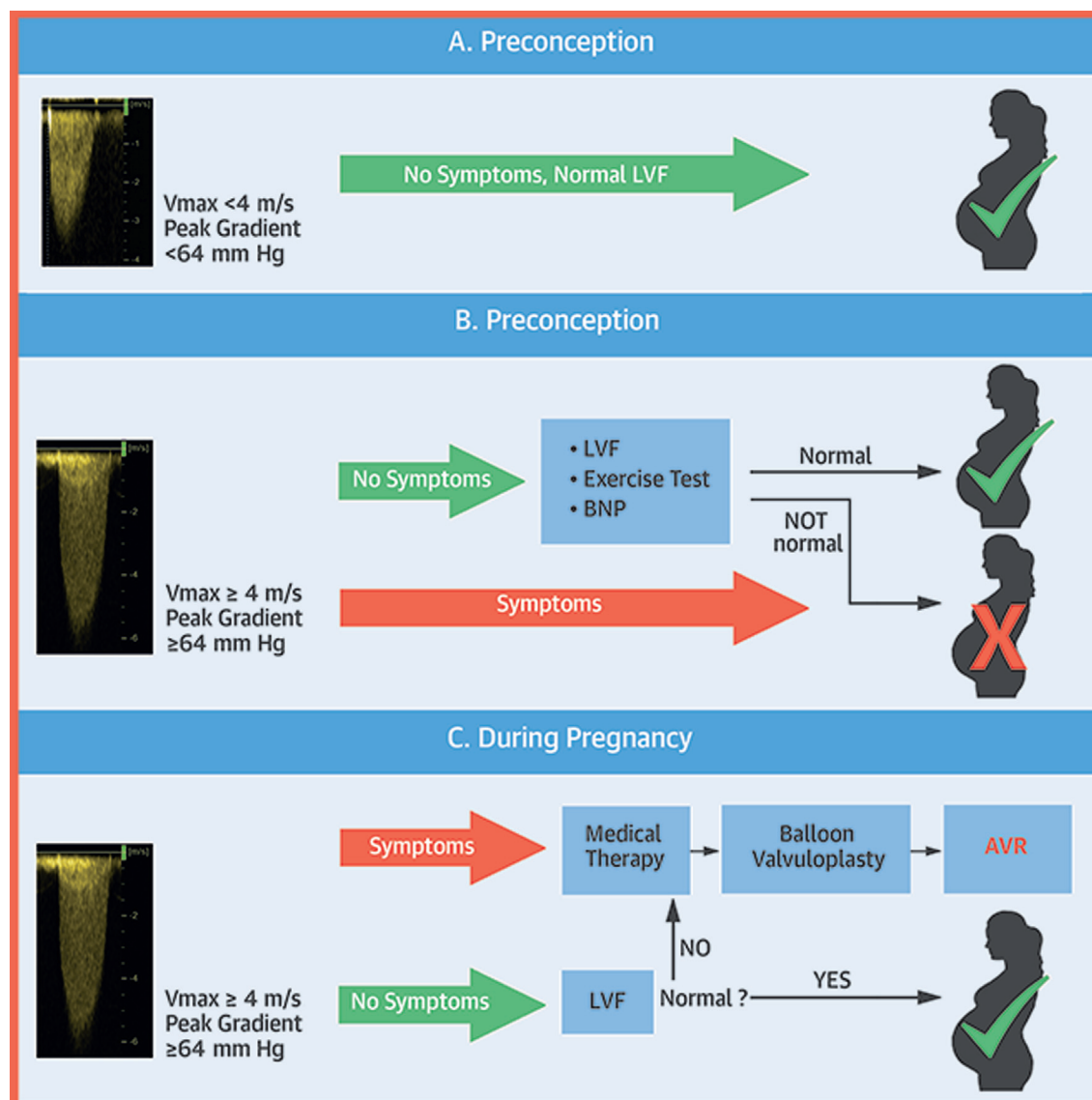
those with severe AS, is close to zero. However, pregnancies may be associated with a relatively high burden of morbidity, such as hospital admissions for cardiac reasons in up to one-third of patients with severe AS. The leading maternal complication during pregnancy was heart failure, which occurred primarily in patients with severe AS who were already symptomatic before pregnancy. By contrast, patients who were asymptomatic before pregnancy, even with hemodynamically severe AS, had a relatively low rate of heart failure occurrence (6.7%). It is alarming, however, that over 50% of patients with severe AS had symptoms before pregnancy, and therefore an indication for valve replacement, emphasizing the need for improvement in cardiac evaluation and appropriate pre-conceptional counseling of patients. Fortunately, heart failure could be managed medically in all but 1 woman. The main predictor of maternal complications, besides symptoms of AS before pregnancy, was the hemodynamic severity of AS. Severe fetal complications were rare, but pre-term birth and a low birth weight were observed in approximately one-third of patients.

It is well recognized that valvular heart disease patients are more likely than other groups of women with structural heart disease to require hospitalization, suffer from supraventricular arrhythmias, or experience postpartum hemorrhagic complications. A previous report using the ROPAC registry found aortic valve disease to be present in 23% of pregnant patients with valvular heart disease, with AS being the

second most common stenotic valve lesion in this cohort (2). Current guidelines consider symptomatic severe AS to be a high-risk condition, and recommend avoiding pregnancy (1,4). In asymptomatic patients, a comprehensive preconception assessment, including an exercise test evaluating physical capacity and blood pressure response to exercise, is recommended (see Central Illustration). This approach is, however, controversial due to absent/limited data regarding the prognostic value of pre-pregnancy exercise testing in the setting of AS (4).

Even women with AS who remain asymptomatic during pregnancy are subject to additional hemodynamic stress at the time of delivery and the immediate postpartum period. These women may therefore become symptomatic at the time of delivery and should be managed in a team approach, including experienced cardiologists, obstetricians, and anesthesiologists. In asymptomatic patients in good clinical condition with normal cardiac function, spontaneous labor is generally preferred to induced labor (1). By contrast, there is less consensus on the recommended mode of delivery in symptomatic patients. Generally, vaginal delivery carries a lower risk of complications for mother and fetus. Compared with Cesarean section, it normally causes smaller shifts in blood volume, less hemorrhage, the absence of abdominal surgery, decreased thrombogenic risk, and fewer infections. Furthermore, the hypertrophied left ventricle in AS may be sensitive to abrupt changes in pre-load (e.g., from anesthetic agents or

CENTRAL ILLUSTRATION Evaluation of Women With Moderate or Severe AS



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(A) and (B) Preconception counseling. Only patients with severe AS and symptoms, or asymptomatic patients with reduced LVF, abnormal exercise test, or high BNP plasma levels should be counseled against pregnancy and AS should be treated. (C) Management of women with severe AS during pregnancy. In case of heart failure symptoms, patients are first treated medically (primarily diuretic agents, in addition to restricting physical activities). If medical treatment is insufficient, percutaneous aortic balloon valvuloplasty can be considered to delay surgical valve replacement until the postpartum period. In case of persistent severe heart failure symptoms, despite valvuloplasty, or when patients are not eligible for valvuloplasty, aortic valve replacement (AVR) should be considered during pregnancy. Asymptomatic patients with normal LVF are followed without treatment. Strenuous physical activities should be avoided. AS = aortic stenosis; BNP = B-type natriuretic peptide; LVF = left ventricular function; Vmax = peak velocity of blood flow across the valve.

hemorrhage). Early epidural analgesia is generally recommended. Cesarean section should be reserved mainly for obstetric indications, or in case of aortic dilation or overt heart failure (1). Nevertheless, in some centers, Cesarean section seems to be a

preferred mode of delivery in women with AS. This may be explained by various factors related to personal physicians' and mothers' preferences, cultural aspects, local standards, and logistical reasons affecting the choice of delivery mode.

Although historic series report maternal mortality rates ranging from 11% to 20% (6,9,15–17), in more recent series, cardiac event rates were lower, with approximately 10% of patients experiencing a cardiac event, and mortality being rare (15,17,18). However, some of these studies also included women with mild AS, diluting the clinically interesting group of patients with moderate/severe AS. The current multinational study of 96 pregnant women followed between 2007 and 2014, and focusing specifically on moderate or severe AS, showed no maternal mortality, thus supporting the notion that maternal morbidity, rather than mortality, is the main clinical problem in this setting. Previous studies suggest a risk of heart failure during pregnancy of approximately 10% (1,15). Our data are consistent with this estimate, showing that heart failure occurred in 11.5% of patients with moderate or severe AS. However, in patients with pre-existing symptoms, pregnancy was complicated by heart failure in 26.3%. Arrhythmias are also a recognized, common complication during pregnancy in this setting, with a reported incidence of 3% to 25% in previous reports (1). In the current series, arrhythmias were also reported as a complication, but with a relatively low rate of around 3%.

Overall, 57% of women included in the current study delivered by Cesarean section. This rate is comparable to that in a recent AS study (18), but higher than the overall Cesarean section rate of 42% reported in the ROPAC registry (19) and in comparison to previous AS studies (17,20). This difference may be related to the current study including a larger proportion of patients with severe AS and a considerable number on anticoagulation. Although current recommendations support vaginal delivery with an assisted second stage of labor in the majority of patients, Cesarean section continues to be advocated by some physicians in women with severe AS and in those requiring anticoagulation (1). Furthermore, country-specific preferences may account for some of the differences, as discussed in detail previously (21).

Severe fetal complications were rare in the current study, but pre-term birth and low birth weight were observed in one-third of patients with severe AS. In addition, newborns of women with severe AS were more likely to have a low Apgar score, to present with low birth weight, and to be small for gestational age. The underlying reasons remain speculative, but are likely multifactorial. Women with severe AS had a significantly shorter pregnancy duration than those with moderate AS (35.5 ± 6.4 vs. 38.0 ± 4.4 ; $p = 0.002$), potentially related to the higher rate of Cesarean section in this setting. In addition, hemodynamic compromise due to AS, resulting in reduced

utero-placental blood flow, is a plausible alternative explanation for the impaired intrauterine fetal growth seen in this study and is supported by the higher prevalence of small for gestational age (accounting for duration of pregnancy) newborns in the severe AS cohort (22).

The most important predictor of both, maternal and fetal adverse events in the current study was the hemodynamic severity of AS. Patients with severe AS had an approximately 2.8-fold increased risk of maternal complications and a 7.6-fold increased risk of fetal complications compared with women with only moderate AS. Interestingly, the peak aortic gradient before pregnancy, as a continuous variable, emerged as the only independent predictor of complications on multivariable logistic regression analysis. This finding, although conceivable, is novel, because previous studies could not confirm a statistical association between baseline severity of AS and outcome in this setting (15,17).

Two women included in this study underwent an aortic valve intervention during pregnancy. Both procedures were successful, and the patients continued to have uneventful pregnancies with vaginal deliveries of healthy babies. This illustrates that in experienced hands, complications can be managed successfully in the current era; however, the risks associated with these procedures (especially of fetal loss) should not be underestimated (23). Therefore, appropriate pre-conceptional assessment and counseling are paramount to avoid pregnancy complications, and to allow for elective procedures to be performed before pregnancy, especially in symptomatic women with severe AS. Nevertheless, the low complication rate in asymptomatic patients, even those with hemodynamically severe AS, supports a conservative approach and avoidance of prophylactic surgery in this group, considering the dilemma of managing pregnancy in the presence of a prosthetic valve (1).

STUDY LIMITATIONS. Due to the multinational nature of the registry, we included pregnancies in developed and emerging countries. We accept that outcomes may be different in the latter setting. However, the vast majority of patients included (74%) were from resource-rich countries of the European Union or from the United States. In addition, obstetric outcomes were not statistically different between the European Union/United States and the remaining countries. On the basis of the hemodynamic inclusion criteria, we also enrolled 13 patients with a mechanical heart valve. It is well appreciated that mechanical heart valves are associated with increased morbidity during pregnancy and worse fetal outcomes (24).

Under hemodynamic aspects, however, we believe that physiological changes during pregnancy should affect prosthetic and native valves similarly. In addition, in this series, no prosthetic valve-related complication was observed. Furthermore, comparing morbidity between patients with severe AS and those with prosthetic valves revealed higher rates of complications in the former group (17.6% vs. 11.5%; 35.3% vs. 20.8%; and 51.5% vs. 35.8% for heart failure and cardiac or all-cause hospitalization, respectively), supporting the notion that the degree of hemodynamic compromise, rather than sequelae related to previous surgery relate to higher rates of complications during pregnancy.

The definition of maternal death used here differs from the published WHO definition by considering mortality during pregnancy and within 7 days of delivery, as opposed to a period of within 42 days of termination of pregnancy recommended by the WHO (25). In contrast to other cardiovascular disorders, such as Marfan syndrome, pulmonary hypertension or cardiomyopathy, mortality beyond 1 week postpartum nevertheless related directly to effect of the pregnancy on the disease is, however, unlikely in AS on the basis of available published reports and our own experience. Thus, longer observation postpartum should not have significantly altered the results. In addition, the causality between pregnancy and later mortality may be difficult to establish in AS.

The current study did not investigate the problem of ascending aortopathy, which is associated especially with bicuspid aortic valve disease. Nevertheless, we did not observe pregnancy-associated aortic dissection in our cohort. Awareness of this potential complication, and appropriate preconception and pregnancy assessment of aortic dimensions should be part of routine care for patients with known bicuspid aortic valve.

Not all of the patients had a pre-pregnancy echocardiographic assessment. We are aware that gradients are expected to increase with increasing cardiac output. Therefore, the classification of AS severity before pregnancy may have been different in some patients with borderline measurements and first presentation during advanced pregnancy (i.e., some of the patients classified to have severe AS during

pregnancy may have had moderate AS if pre-pregnancy data had been available).

CONCLUSIONS

The current multinational study, including 96 women with at least moderate AS managed in the current era during pregnancy, highlights the ongoing challenge of pregnancy in this setting. Although, the maternal mortality rate was zero in this cohort, hospitalizations for cardiac reasons were frequent, and both pre-term birth and low birth weight were observed in one-third of patients with severe AS. The fact that heart failure, the most frequent maternal complication, occurred predominantly in patients with severe AS who had at least mild symptoms, indicating intervention already before pregnancy, emphasizes the importance of appropriate pre-conception patient evaluation and counseling.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Pregnant women with severe AS face a low risk of mortality, but those with severe AS and symptoms before pregnancy have high rates of cardiac hospitalization.

TRANSLATIONAL OUTLOOK: Further studies are warranted to determine whether appropriate evaluation and counseling of women with AS before conception reduces maternal and fetal complications.

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KEY WORDS fetal outcome, heart failure, maternal outcome, risk factors

APPENDIX For a complete list of the ROPAC investigators, please see the online version of this article.